EPIDEMIOLOGICAL STUDY

Risk factors for severe outcome of cases with pandemic influenza A(H1N1)pdm09

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Abstract

OBJECTIVES: The aim of this study is to describe demographic, clinical and epidemiological characteristics of cases with laboratory-confirmed pandemic influenza virus A(H1N1)pdm09 reported in Slovakia from May 28, 2009 to December 30, 2009 and analyse the association between risk factors and severe outcome of these cases.

BACKGROUND: In the spring of 2009, an outbreak of a pandemic influenza virus A(H1N1)pdm09, emerged in Mexico and spread globally. Until December 2009, 1,014 cases were notified in Slovakia.

METHODS: The data were collected within national influenza surveillance system. Odds ratios (95% CI) were calculated. Associations were found to be significantly associated with the worse outcome (p < 0.05) in the univariate analysis and were adjusted for possible effects of age and sex by using a logistic regression model.

RESULTS: Out of the total number of 1,014 cases, 131 (12.9 %) cases were hospitalized, and 43 (4.2 %) of those were admitted to intensive care units. During the reporting period, 38 deaths were reported, representing a case fatality rate of 3.75 %. The median age of severe cases (35 years, IQR = 29 y) was significantly higher than the median age of mild cases (24 years, IQR = 19 y; p < 0.001). By using a logistic regression, we found out that chronic obstructive pulmonary disease (COPD) (aOR = 9.2; 95%CI: 1.42–59.98), cardiovascular diseases (aOR = 14.97; 95%CI: 5.49–40.79), malignity (aOR = 7.6; 95%CI: 1.95–29.37) and gravidity (aOR = 55.21; 95% CI: 14.40–211.58) were significantly associated with severe outcomes of the cases.

CONCLUSION: The fact, that 35% of severely ill patients did not report any risk factor suggests the importance of vaccination as a prevention of influenza *(Tab. 2, Fig. 1, Ref. 18)*. Text in PDF *www.elis.sk*.

KEY WORDS: pandemic influenza A(H1N1)pdm09, risk factor, severe outcome of the disease.

Introduction

In the spring of 2009, an outbreak of respiratory disease caused by a new type of influenza virus, later identified as a pandemic influenza virus A(H1N1)pdm09, emerged in Mexico and spread globally (1). On April 25, 2009, the World Health Organization (WHO) recognized the outbreak as a public health emergency of international concern under the International Health Regulation (2). On June 11, 2009 WHO director-general raised the level of influenza pandemic alert to the phase 6 (3).

After the alert of WHO and European Centre for Disease Prevention and Control (ECDC) at the end of April 2009, Slovakia intensified The National Influenza Surveillance System in order to detect first cases (4), which happened on May 25, 2009 (4). During the early phase of the pandemic, Slovakia, as other European countries, reported daily case-based and aggregated data to ECDC through the Early Warning and Response System (EWRS). After the week 39/2009, Slovakia reported data weekly and in a new format. Since November 2009, a hospital sentinel surveillance of severe acute respiratory infection (SARI) was established (4).

The need for new research on pandemic influenza has been recently declared (5).

In this article we describe demographic characteristics, clinical symptoms and risk factors for severe outcome of cases with laboratory-confirmed pandemic influenza virus A(H1N1)pdm09 reported in Slovakia between May 28, 2009 and December 30, 2009 and analyze the association between risk factors and severe outcome of the cases.

Methods

Inclusion criteria

Eligible cases included adults and children with clinical symptoms of influenza with laboratory-confirmed pandemic influenza virus A(H1N1)pdm09 reported in Slovakia from May 28, 2009 to December 30, 2009. The laboratory confirmation method was based on reverse transcription polymerase chain reaction (RT-PCR) or real-time reverse transcription polymerase chain reaction (rRT-PCR).

Risk factor for severe outcome was defined as allergy, any pulmonary disease, asthma, COPD, cardiovascular disease, malignity, neuromuscular disease, diabetes mellitus, chronic renal insufficiency, chronic hepatic disease, obesity (BMI 30–40), gravidity, immunodeficiency (except HIV), HIV, leucopenia and hematuria.

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The outcome of case was defined as severe when symptoms of influenza with laboratory-confirmed pandemic influenza virus A(H1N1)pdm09 required hospitalization at intensive care unit (i.e. ICU) and/or the patient developed pneumonia and/or died.

Data collection

The data on pandemic influenza cases were reported in two ways. Local epidemiologists reported the cases to the Department of Epidemiology at Public Health Authority of the Slovak Republic (PHA SR) by phone or e-mail and they simultaneously entered those cases into the Epidemiological Information System. The following data were collected: demographic data, clinical characteristics, underlying risk conditions for severe outcome, treatment, outcome of illness, and vaccination status.

Two databases were merged based on personal identificators (identification number or birth date and name).

Analysis

The data analyses were performed by using STATA 10.5.

Odds ratios with 95% confidence intervals were used as the measure of association between risk factor and outcome of illness (severe vs. non-severe outcome).

Associations were found to be significantly associated with the worse outcome ($p < 0.05$) in the univariate analysis and were adjusted for possible effects of age and sex by using a logistic regression model

Results

From May 28, 2009 to December 30, 2009, a total number of 1,014 cases were notified to the PHA SR, leading to a cumulative
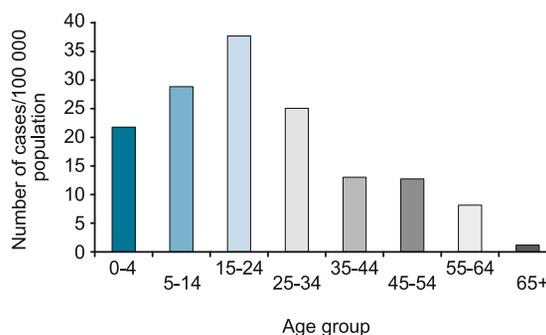

Fig. 1. Age-specific incidence of cases with laboratory-confirmed virus of pandemic influenza. *Data on age were missing in 3 cases.

incidence of 18.7 per 100,000 population. Of 1,014 cases, 131 (12.9 %) were hospitalized, of which 43 (4.2 %) required admission to intensive care unit (ICU). Thirty-eight cases died (incidence: 0.7/100,000 population; case-fatality rate: 3.75 %).

Demographic characteristics

The median age of cases was 25 years (range: 0–89 years). The most affected age group was 15–24 years with the number of cases 297 (29.3 %; 37.7/100,000 population). The least affected were cases aged 65 years or older with the number of cases 8 (0.8 %; 1.2/100 000 population) (Fig. 1).

The median age of deceased cases was 36 years (range: 0–66 years). The highest number of cases died in the age group of 45–54 years with the number of cases 9 (23.7 %; 1.2/100,000 population). The lowest number of cases died in the age group

Tab. 1. Risk factors of cases with laboratory-confirmed virus of pandemic influenza A(H1N1)pdm09 in Slovakia by outcome, 2009 (n =1014).

Risk Factor (RF)	Severe Outcome n=57	Non-severe Outcome n=957			
	n[a] / N[b] (%)	n / N[b] (%)	Adjusted OR	95% CI	p value
Demographic characteristics					
Median age	35	24	1.03	1.01–1.04	0.010
Female	30/57 (52.63)	485/957 (50.68)	–	–	–
Underlying conditions					
Pulmonary disease	9/57 (15.79)	26/957 (2.71)	2.44	0.64–9.37	0.194
Asthma	1/57 (3.51)	21/957 (2.30)	–	–	–
COPD[c]	6/57 (10.53)	5/957 (0.52)	9.16	1.42–59.98	0.020
Cardiovascular disease	11/57 (19.30)	10 /957 (1.04)	14.97	5.49–40.79	0.000
Malignity	4/57 (7.27)	9/957 (0.94)	7.58	1.95–29.37	0.003
Neuromuscular disease	1/57 (1.75)	8/957 (0.84)	–	–	–
Diabetes mellitus	4/57 (7.02)	5/957 (0.52)	5.35	0.91–31.31	0.063
Chronic renal insufficiency	2/57 (3.51)	5/957 (0.52)	–	–	–
Chronic hepatic disease	1/57 (1.75)	3/957 (0.31)	–	–	–
Obesity (BMI 30–40)	3/51 (5.88)	1/38 (2.63)	–	–	–
Gravidity	6/14 (42.86)	6/308 (1.95)	22.17	4.36–112.64	0.000
Allergy	0/7 (0.00)	16/288 (5.56)	–	–	–
Immunodeficiency (except HIV)	0/7 (0.00)	4/288 (1.39)	–	–	–
HIV	0/7 (0.00)	1/288 (0.35)	–	–	–
Leucopenia	0/7 (0.00)	1/288 (0.35)	–	–	–
Hematuria	0/7 (0.00)	1/288 (0.35)	–	–	–

[a] Number of cases with particular characteristic
[b] Number of cases with data available
[c] Chronic obstructive pulmonary disease
[d] Number of women of childbearing age (i.e. 15–44 years) as denominator

Tab. 2. Number of risk factors of cases with laboratory-confirmed virus of pandemic influenza A(H1N1)pdm09 in Slovakia by outcome, 2009 (n=1014).

Number of Risk Factors (RF)	Severe Outcome n=57	Non–severe Outcome n=957			
	n / N (%)	n / N (%)	Adjusted OR	95% CI	p value
0 RF	20/57(35.09)	859/957(90.51)	0.08	0.04–0.15	0.000
1 RF	30/57 (52.63)	92/957 (8.86)	3.28	1.01–10.66	0.048
2 and more RFs	7/57 (12.28)	6/957 (0.63)	8.58	4.80–15.32	0.000

of 65 years or older with 1 deceased case (2.6 %; 0.2/100 000 population).

Male-to-female ratio was 1.03:1. Out of 515 women, 322 were of childbearing age and 12 of them (3.73 %) were pregnant.

Clinical characteristics

Data on clinical characteristics were available in 382 (37.7 %) cases. The most common symptoms included fever (n = 324; 84.8 %) and acute respiratory symptoms such as cough, sore throat, coryza (n = 322; 84.3 %), followed by headache (n = 161; 42.1 %), myalgia (n = 160; 41.9 %) and arthralgia (n = 135; 35.3 %). Shortness of breath was reported in 47 (12.3 %) cases, and fatigue in 39 (10.2 %) cases. Gastrointestinal symptoms were observed in 37 (9.7 %) cases.

Underlying conditions

The most common underlying conditions of the cases included allergy 19/295 (5.4 %), obesity 4/89 (4.5 %), gravidity 12/322 (3.7 %), pulmonary disease 35/1,014 (3.5 %), asthma 22/1,014 (2.2 %), cardiovascular disease 21/1,014 (2.1 %), immunodeficiency except HIV 4/295 (1.4 %), malignity 13/1014 (1.3 %), COPD 11/1,014 (1.1 %), neuromuscular disease 9/1,014 (0.9 %), diabetes mellitus 9/1,014 (0.9 %) Seven patients had chronic renal insufficiency (0.7 %) and four patients had chronic hepatic disease (0.4 %). Other underlying conditions were in single cases, namely HIV, leucopenia and hematuria.

Association of risk factors with severe outcome

Among the total number of 1,014 cases included in our study, 57 (5.6 %) cases had a severe outcome. Forty-three cases were admitted to ICU (20 cases had pneumonia and died; 4 cases had pneumonia and survived; 9 cases died from reasons other than pneumonia; 10 cases were admitted to ICU for reasons other than pneumonia and survived); 14 cases were admitted to departments other than ICU (5 cases had pneumonia and survived; 9 cases died from reasons other than pneumonia).

None of the 57 cases with severe outcome were vaccinated against seasonal influenza. Vaccination against pandemic influenza was not yet available at that time in Slovakia.

We conducted a multivariate analysis with the risk factors, which were significant in the univariate analysis: any pulmonary disease, COPD, cardiovascular disease, malignity, diabetes mellitus, and gravidity. Chronic obstructive pulmonary disease (COPD), cardiovascular disease, malignity and gravidity were independently associated with the severe outcome. Study patients with severe outcome were 9.16-fold (95% CI: 1.42-59.98, p=0.020) more likely to have a COPD, 14.97-fold (95% CI: 5.49–40.79, p = 0.000) more likely to have a cardiovascular disease, 7.58-fold

(95% CI: 1.95–29.37, p = 0.003) more likely to have a malignity and 22.17-fold (95% CI: 4.36–112.64, p = 0.000) more likely to be pregnant than study patients with non-severe outcome.

There was no association found between pulmonary disease, asthma, neuromuscular disease, diabetes mellitus, chronic renal insufficiency, chronic hepatic disease, obesity, allergy, and immunodeficiency except HIV, HIV, leucopenia, hematuria and severe outcome (Tab. 1).

After adjusting for age and sex, the absence of risk factors seems to have a protective effect on the disease severity (aOR = 0.08, 95% CI: 0.04–0.15, p = 0.000). Study patients with severe outcome were 3.28-fold (95% CI: 1.01–10.66, p = 0.048) more likely to have 1 risk factor and 8.58-fold (95% CI: 4.80–15.32, p = 0.000) more likely to have 2 and more risk factors compared to study patients with non-severe outcome (Tab. 2).

Discussion

This study describes demographic, clinical and epidemiological characteristics of cases with laboratory-confirmed pandemic influenza virus A(H1N1)pdm09 reported in Slovakia from May 28, 2009 to December 30, 2009, and analyses the association between risk factors and severe outcome of these cases.

During the study period, a total number of 1,014 cases were notified to PHA SR, leading to a cumulative incidence of 18.7 per 100,000 population. However, the estimation of real incidence was much higher. The disease had an uncomplicated clinical course in most patients (94.4 %) and therefore many patients did not seek medical care. Not all patients who had sought the medical care underwent laboratory tests, and the virus was not successfully proven in all samples tested. Out of 1,014 cases, 131 (12.9 %) were hospitalized, of which 43 (4.2 %) required admission to an intensive care unit (ICU). Thirty-eight cases died (incidence: 0.7/100,000 population; case-fatality rate: 3.75 %).

In accordance with the results of other studies from France, USA and Netherlands (6, 7, 8) and as opposed to seasonal influenza, most of the cases occurred in young and middle-aged adults. Highly affected was the youth group aged 15–24 years. The proportion of 62.3 % of all cases occurred in the age group of 15–44 years, while less than 1 % of adults aged over 64 years were affected. Experts explain this by pre-existing immunity of persons born before 1957 (8, 9, 11, 12). When comparing the clinical course of the disease and its association to age, cases with severe outcome were significantly older (median age 35 years) than cases with non-severe outcome (median age 24 years). These observations are consistent with other studies from California, Australia and UK (10, 11, 12) The presence of these chronic underlying

conditions can worsen the clinical course of influenza illness in both seasonal and pandemic types of influenza. Most of the deaths (97 %) occurred in cases aged less than 64 years, as described in UK (12, 13).

The symptoms recorded in the majority of cases, such as fever (84.8 %) and acute respiratory symptoms (84.3 %), as well as other symptoms (headache, arthralgia and myalgia) were not different from the classical picture of seasonal influenza (7, 15). Gastrointestinal symptoms reported elsewhere (7, 10, 14, 15) as being characteristic for the pandemic influenza infection were reported only in 37 (9.7 %) cases. Dyspnoe was reported in 47 cases and it may be explained by the later development of pneumonia or by the exacerbation of chronic underlying conditions like asthma, or COPD or cardiovascular disease.

The most commonly reported risk factors in our study, such as allergy (5.4 %), obesity (4.5 %), gravidity (3.7 %), pulmonary disease (3.5 %), asthma (2.2 %), and cardiovascular disease (2.1 %), are in line with the studies from other countries (6, 7,10).

As mentioned above, the clinical course of most Slovak patients n = 957 (94.4 %) was uncomplicated. This is consistent with the reports elsewhere (16, 17). A severe outcome was observed in 57 (5.4 %) cases while 75 % of them were admitted to ICU; pneumonia developed in 51 % of cases, and 67 % of cases with severe outcome died.

In multivariate analysis, we found that COPD, cardiovascular disease, malignity and gravidity were independent risk factors for severe outcome of cases. COPD and cardiovascular disease are generally accepted risk factors for severe outcome of patients with pandemic and seasonal types of influenza (18). Unlike other countries, but in line with the data reported from Netherlands, obesity was not a risk factor for disease severity in Slovakia. Twelve pregnant women were included in our study group. In addition to pregnancy, they did not report any other risk factors and they have not been vaccinated against seasonal flu. Five of them were admitted to ICU and all 5 died.

In our study patients, the increase in number of risk factors was significantly associated with severe outcome of illness. However, 20 patients (35 %) with severe outcome had no risk factor, which in line with the results of a study carried out in France (6) points out that the pandemic influenza virus can cause a very serious disease even in humans without any risk factors. Median age of these patients was 30 years.

The study has several limitations. While at the beginning of the pandemic, all cases underwent laboratory tests and were reported, in the later stage only severe cases underwent laboratory tests and were reported. The major limitation of the study was data incompleteness. Due to this we could not analyze the effect of antiviral therapy on the disease course. For the same reason, we also did not analyze the data on complications (i.e. dehydration, development of ARDS) of the course of the disease. The data were collected only as to whether the patient required mechanical ventilation or oxygenotherapy. Thirty-five (61.4 %) out of 57 patients with severe outcome were treated with either mechanical ventilation or oxygenotherapy. Extracorporeal membrane oxygenation (ECMO) was not used in Slovakia.

Our study confirms the role of COPD, cardiovascular disease, malignity and gravidity as risk factors for severe outcome of cases with pandemic influenza. One third of young completely healthy adults developed severe illness. This indicates that the role of preventive public health measures such as vaccination is of importance.

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